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(54) Controlled release drug delivery device.

(57) An oral drug delivery device for delivering a drug either intermittently or to a pre-selected region of the gastro-intestinal tract, particularly to the colon, consists of an a solid core comprising an active agent coated with a delay jacket, then coated with a semi-permeable membrane which is optionally drilled to provide a release orifice, and then optionally further coated with an enteric material. The device delivers substantially all of the active agent to the targeted site.

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The present invention relates to tablets which are time-controlled to release active agent intermittently or at a pre-selected region of the gastro-intestinal tract, specifically the colon.

Parametric drug delivery refers to drug release in synchrony with its temporal requirements or optimal absorption site, thereby maximizing therapeutic effect while simultaneously minimizing side-effects or *in vivo* degradation. An example of parametric drug delivery is delivery of a drug to a pre-selected region of the gastro-intestinal tract, such as the colon. Another example is delivery of a drug intermittently at pre-selected times such that the patient receives the drug when needed.

Delivery of a beneficial drug in the colon has been the goal of research projects. Many drugs are rendered ineffective by the enzymes present in the fluids of the upper gastro-intestinal tract, particularly protein or peptide-like drugs. Some drugs are more readily or more predictably absorbed by the colonic tissue than by that in the upper gastro-intestinal tract.

Delivery of a beneficial drug in the colon is also therapeutically indicated to treat diseased colonic tissue. In such circumstances, the drug should not be absorbed prior to localization in the colon lest its concentrations be diminished or even depleted prior to reaching the intended site of action. Such treatment would be beneficial for a variety of colonic diseases including inflammatory bowel disease, colitis ulcerosa, enteritis, regionalis Crohn, chronic nonspecific colitis, and diverticulitis.

Prior treatments have been attempted rectally using suppositories and enemas. Rectal administration, while often more effective than oral administration, is limited in that most rectally administrable dosage forms are capable of producing the intended result only in the immediate area, not reaching the upper portions of the colon. This is because the length of the colon reached is volume dependent, usually reaching only as far as the splenic flexure. Furthermore, if the patient suffers from severe inflammation of the rectum, he may experience difficulty with retention enemas.

An orally administrable dosage form to treat colonic diseases would usually be preferred and is often required. Orally administrable treatments, using tablets, capsules, and the like, have been attempted. However, to reach the colon intact, the dosage form must withstand the rigors of the transit through the gastro-intestinal tract. These rigors include at least a million-fold variation in hydrogen ion concentration, wide variations in osmotic pressure from the surrounding fluids, a variety of enzymes, and a strong mechanical grinding force.

Most of these orally administered dosage forms result in delivery of the drug in the upper portion of the gastro-intestinal tract or, in the case of controlled release dosage forms, deliver drug throughout the entire length of the gastro-intestinal tract instead of concentrating delivery primarily within the colon. Thus, in either case, by the time the dosage form reaches the colon, the drug concentration is diminished or even depleted. In addition, the acidic and enzymatic environment of the stomach may inactivate a substantial amount of the drug, particularly protein or peptide-like drugs. Even if the drug is released from the stomach in its active state, such drugs frequently are metabolized or inactivated in the small intestine. Thus, little if any of the drug from these conventional dosage forms is available for producing a therapeutic result in the colon, especially if the dosage form reaches the colon essentially devoid of drug.

Drug delivery to the colon is also difficult because of the uncertainty of the transit time from oral ingestion to arrival at this pre-selected site. The time of retention within the stomach is most variable, depending both on the size of the dosage form and the amount of food present at the time of ingestion. The drug delivery device may remain within the stomach from about 0.5 to about ten hours. The device then enters the small intestine where retention time is significantly more constant and less dependent upon the amount of food present. It takes from about three to about six hours to travel the length of the small intestine to the beginning of the colon. The device may then remain within the colon from about ten to about fourteen hours in a subject with normal motility.

The time span necessary to delay release of the drug from an orally administered dosage form until the beginning of the colon is wide. This time span can be considerably narrowed by measuring the time from arrival in the small intestine instead of from the time of ingestion. Drug delivery in the stomach may be prevented by the use of an enteric coating which is resistant to the gastric fluids. As such a coating is not soluble in fluids with an acidic pH, such as that of the stomach, application to the outside of the dosage form inhibits release prior to reaching the higher pH of the small intestine. Once the dosage form reaches the small intestine and the enteric coating dissolves, drug release needs to be delayed only an additional three to six hours to result in substantially no active agent being delivered before the colon.

Although some drug may reach the colon passively, conventional peroral dosage forms are not designed to deliver their contents specifically to the colon. Generally, they are formulated to be immediate release devices which disintegrate in the stomach, duodenum, or small intestine, allowing the drug to be immediately exposed to the local environment.

Controlled release dosage forms are known, for example Oral Osmotic Systems or OROS® (Alza Corporation). Although the benefits of controlled release are significant, such as reduction in the number of doses

and steady drug levels in the blood, they are generally no more effective than conventional tablets in delivering the active agent primarily to the colon.

Several delivery forms have been developed which attempt to deliver active agent primarily to the colon. These methods rely upon either the environmental conditions surrounding the system, particularly pH, bacterial count and/or time.

Wong, et al. (US Patent Nos. 4,627,851; 4,693,895; and 4,705,515) disclose a tri-laminated core in which the first layer is composed of an insoluble, but semi-permeable composition, the second is a microporous combination of water insoluble polymer and osmotic solute, and the third contains an enteric composition. This dosage form has a delayed onset of delivery for a period of about two hours after it exits the stomach, after which only about 50% of the drug is released within twenty-four hours. This drug delivery time scheme is insufficient to insure that the bulk of the drug is delivered to the colon.

Theeuwes et al. (U.S. Patent No. 4,904,474) disclose a dosage form which has a two-layered internal compartment with a first layer of the drug in an excipient layer adjacent to an exit passageway and a second layer of a push component. The internal compartment is surrounded by a semi-permeable wall and then an enteric layer. This dosage form results in a delay of the onset of delivery in intestinal fluid for a period of about two hours. This represents a delay period too short, and a delivery rate too slow to insure the bulk of the drug is delivered to the colon.

Ring, et al. (WO 91/07949) disclose a tablet core coated with two laminates. The outer laminate is an erodible acrylic polymer and the inner laminate consists primarily of amylose in the glassy state which can only be degraded in the presence of fecal microflorae.

The instant parametric drug delivery devices can also be used to deliver a drug intermittently at pre-selected times such that the patient receives the drug when needed. This is of particular importance in treating diseases which have symptoms which do not remain constant throughout the day and night.

Blood pressure is known to follow a circadian rhythm during a 24-hour period. In some subjects the highest pressure occurs in the morning shortly after the individual awakes, suggesting that it would be appropriate to deliver an antihypertensive agent such as a β-blocker to such a patient sufficiently before awakening so as to mitigate the effects of the disease at the most appropriate time interval. In order to accomplish this without disturbing the patient's sleep, it is necessary to administer the drug in the evening in a form that is activated just before the patient arises.

It is accordingly an object of the present invention to provide a delivery device for the oral administration of a pharmaceutically acceptable active agent to a warm-blooded animal, either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon.

It is another object of this invention to provide a dosage form for delivering substantially all of a therapeutic drug to the colon.

It is yet another object of this invention to provide a dosage form which comprises a core tablet coated with a delay jacket for delaying the delivery of the drug to insure the time required for the dosage form to travel through the small intestine.

It is still yet another object of this invention to provide a dosage form in which the semi-permeable membrane is still strong enough to resist the hydrostatic pressures of the osmotic core.

It is a further object of this invention to provide a dosage form which comprises an enteric coating over a semi-permeable wall for further delaying the delivery of the active agent during the time required for the dosage form to travel through the stomach.

It is still a further object of this invention to provide a dosage form which resists dissolution in gastric fluid for at least two hours, further delays initiation of active agent release for at least three hours, and releases at least 70% of its active agent within twenty-four hours.

It is yet still a further object of this invention to provide a delivery device which delivers drug intermittently at pre-selected times.

These, and other objects are accomplished by the present invention which pertains to an osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon. This drug delivery device comprises:

a) a solid core comprising an active agent;

b) a delay jacket coated over the core;

c) a semi-permeable membrane coated over the delay jacket, the membrane optionally having a release orifice; and optionally

d) an enteric coating over the semi-permeable membrane.

Such device resists dissolution in gastric fluid for at least two hours and thereafter limits the release of

active agent in intestinal fluid to approximately ten percent or less for at least three hours after the device passes through the pylorus due to the delay jacket. The device thus allows for controlled continuous release of the active agent in the pre-selected region of the gastro-intestinal tract at a predetermined average rate, preferably at a rate of about 5 percent to about 25 percent by weight per hour. In addition, the device allows for substantially all of the active agent to be released at the pre-selected region of the gastro-intestinal tract, preferably 70-100% within twenty-four hours of ingestion.

Preferably, the device releases its active agent *in-vitro* according to the following scheme, where time is hours from inception corresponding to *in-vivo* release of active agent from time of ingestion:

Time (hrs.)	Fluid	Total Amount Released (%)
2 gastric	0 - 4	
5 intestinal		0 - 10
6 intestinal		0 - 20
8 intestinal		0 - 50
10 intestinal		10 - 80
12 intestinal		20 - 100
18 intestinal		50 -109
24 intestinal		70 -115

Thus, the colonic delivery device would deliver from about 50% to about 100%, more particularly from about 60% to about 90%, most particularly from about 70% to about 80% of its active agent to the colon.

The solid core comprises an active agent and may optionally include other pharmaceutically acceptable excipients including osmotic agents, lubricants, glidants, wetting agents, binders, fillers, and suspending/thickening agents. Any core which would be suitable for an oral osmotic system may be used in the present invention, including the various modifications currently known in the art such as push-pull OROS.

Active agents useful in the core include, but are not limited to, proteins and peptides, antiasthmatics, antianginals, corticosteroids, 5-lipoxygenase inhibitors, antihypertensives, and leukotriene B_4 receptor antagonists. Proteins and peptides include, but are not limited to, transforming growth factors (TGF), immunoglobulin E (IgE) binding factors, interleukins, interferons (IFN), insulin-like growth factors (IGF), milk growth factors, anticoagulants, and parathyroid hormones (PTH). Specific active agents include theophylline, IGF-I, PTH (1-34) and analogues thereof, TGF_{α}, $TGF_{\beta 1}$, $TGF_{\beta 2}$, $TGF_{\beta 3}$, IFN_{α}, hybrid IFN_{α}, IFN_{γ}, N-hydroxy-N-((6-phenoxy-2H-1-benzopyran-3-yl)methyl)-urea, 4-[5-[4-(aminoiminomethyl)phenoxy]pentoxy]-3-methoxy-N,N-bis(1-methylethyl)-benzamide-(Z)-2-butenedioate, N-[2-[[2-[[4-(4-fluorophenyl)phenyl]methyl]-1,2,3,4- tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxyurea, 1-(1-benzo[b]thien-2-ylethyl)-1-hydroxyurea, 5-[2-(2-carboxyethyl)-3-{6-(para-methoxyphenyl)-5E-hexenyl}oxyphenoxy]valeric acid, hirudin, heparin, calcitonin, 5-aminosalicylic acid, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, metoprolol fumarate, metoprolol tartrate, tetrahydroaminoacridine (THA), galanthamine, ursodiol, clomipramine hydrochloride, terbutaline sulfate, aminoglutethimide, deferoxamine mesylate, estradiol, isoniazid, methyltestosterone, metyrapone, and rifampin. Of particular importance are theophylline, IGF-I, PTH (1-34) and analogues thereof, TGF_{α}, $TGF_{\beta 1}$, $TGF_{\beta 2}$, $TGF_{\beta 3}$, IFN_{α}, hybrid IFN_{α}, IFN_{γ}, hirudin, heparin, calcitonin, 5-aminosalicylic acid, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, and metoprolol. Virtually any other active agent which is known to be colonically absorbable or used to topically treat the colon can be used as an active agent in the present invention as long as it is compatible with the system components.

The core may include an osmotic agent if necessary or desirable to effect the desired release profile. The active agent, for example, metoprolol fumarate, may be sufficiently soluble to induce an internal hydrostatic pressure acceptable to eliminate the need for any additional osmotic agent. Suitable osmotic agents include pharmaceutically acceptable salts of inorganic and organic acids or nonionic organic acids of particularly high water solubility, e.g. carbohydrates such as sugar, or amino acids, or another active agent possessing suitable solubility.

Examples of water-soluble compounds for inducing osmosis in the core include inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts

of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof.

Additional core excipients include tabletting lubricants, glidants, wetting agents to aid in dissolution of the components, binders, and suspending/thickening agents. Suitable lubricants include calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate. Suitable glidants include fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents include, but are not limited to, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9 or 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, 40, 60, or 80, sodium lauryl sulfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol (4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane). Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethyl cellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polyvinylmethacrylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable suspending/thickening agents include acacia, agar, alginic acid, bentonite, carbomer, carboxymethyl cellulose calcium, carageenan, carboxymethyl cellulose sodium, corn starch, dextrin, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, lecithin, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, pectin, poloxamer, polyethylene glycol alginate, polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, vinyl acetate, powdered cellulose, pregelatinized starch, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, and xanthan gum.

The delay jacket is included to impede the dissolution and release of the active agent for the time necessary for the drug delivery device to travel through the small intestine. The delay jacket is capable of attracting water across the semi-permeable membrane while also hindering the water from reaching the active core for the designated period of delay. The delay jacket will typically contain both water soluble, osmotically active components and insoluble and/or swellable components. The soluble osmotic agents leach out of the jacket and a suspension of at least some of the insoluble and/or swellable components remains. The active agent will later diffuse through this remaining suspension and thus the release of the active agent is dependent not only upon the composition of the inner core, but also upon the composition of the jacket.

The delay jacket comprises a binder, an osmotic agent, and a tablet lubricant. Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polyvinylmethacrylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable osmotic agents include, but are not limited to, inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof. Suitable tablet lubricants include calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Additional jacket excipients may include glidants and wetting agents. Suitable glidants include, but are not limited to, fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9 or 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20 or 40, polysorbate 60 or 80, sodium lauryl sulfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol® (4-(1,1,3,3-tetramethylbutyl)phenol) polymer with formaldehyde and oxir-

ane).

Certain excipients may be included within the device to serve more than one function. For example, glucose may be included as a binder and/or an osmotic agent, and talc may be included as a glidant and/or a lubricant.

The delay jacket may be applied to the core using conventional means known in the technology, for example by using a tablet press or a spray coater. If applied as a solid, the delay jacket is preferably between about 125% and about 275%, and more preferably between about 150% and about 250% of the core by weight. If applied as a liquid, the delay jacket is between about 10% and about 100%, or between about 20% and about 80%, and preferably between about 30% and about 60% of the core by weight. However, in both cases the ranges may vary based on the solution/suspension properties of the materials selected, and on the permeability properties of the rate controlling membrane.

The semi-permeable membrane is intended to be rigid enough so as to maintain the physical integrity of the tablet of the invention even in its environment of use without adversely affecting the active agent. The term "semi-permeable," as defined herein, refers to a membrane which, under identical conditions, transports different molecular species at different rates. In this case, the membrane is permeable to gastro-intestinal fluids, but is less permeable to the active agent or osmotic agent. If it is less permeable to the solubilized or suspended active agent or osmotic agent, it is necessary to include at least one release orifice through the membrane, while if it is permeable to the active agent or osmotic agent, the release orifice is optional.

The membrane comprises a material which can form films and typically comprises any of the porous membrane materials known in the tabletting art. Typical materials for forming the membranes are those known in the art to form osmosis or reverse osmosis membranes, including polycation-polyanion membranes. The porous membrane materials include cellulose acetate, ethylcellulose, polymethacrylic acid esters and acrylic acid ester/methacrylic acid copolymer with quarternary ammonium groups, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose ethers, cellulose acetate propionate, polyvinyl methyl ether polymers, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluene sulfonate, triacetate of locust bean gum, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated ethylenevinylacetate, polymeric epoxides, alkylene oxide-alkyl glycidyl ethers, polyurethanes, and polyglycolic acid. Preferably, the membrane material is cellulose acetate, ethylcellulose, polymethacrylic acid esters and acrylic acid ester/methacrylic acid copolymer with quarternary ammonium groups.

Alternatively, the semi-permeable membrane may be comprised of non-porous membrane materials in which pores have been formed. This is accomplished by including a water soluble pore-forming material in the insoluble, non-porous membrane material solution. When the membrane is exposed to an aqueous environment, the pore-forming material dissolves, resulting in the formation of pores. Thus, the porosity of the membrane is directly proportional to the amount of pore-forming material incorporated into the membrane. The non-porous membrane materials include acrylics, polyurethanes, silicones, polyethylenes, polyvinyl chlorides, and ethylcellulose. The pore-forming materials include lactose, sucrose, mannitol, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and surfactants or other soluble additives.

The semi-permeable membrane may be applied using conventional film coating techniques known in the art, for example fluidized bed spraying. The choice of semi-permeable membrane plays an important role in controlling the release of the active agent. For example, it is known that the acetyl value is an important factor in determining the release rate from membranes constructed from cellulose acetate. Compendial grade cellulose acetate is commercially available with nominal acetyl values of either 32% or 40%. Membranes constructed from material at 32% acetyl value release drug from similar drug cores at a faster rate than do membranes constructed with the same amount of cellulose acetate by weight having a 40% acetyl value.

Preferred membrane materials include methacrylic ester copolymers, poly(ethyl acrylate, methyl methacrylate), for example EUDRAGIT® NE 30 D, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), for example, EUDRAGIT® RL or EUDRAGIT® RS, polymethyl methacrylate-methacrylic acid copolymers, cellulose acetate, and ethylcellulose, and combinations thereof.

One or more release orifices may be included through the semi-permeable membrane. This release orifice is included to allow passage of the active agent and the soluble excipients, either in addition to or as an alternative to the pores of the semi-permeable membrane. It can be used to further control the release rate of the active agent by varying its size. Typically, the size of the release orifice is between about 0.05mm and about 1.5mm, more narrowly between about 0.15mm and about 0.40mm.

The enteric coating is included to prevent the dissolution of the jacket and core in the stomach. It may consist of any pharmaceutically acceptable material which is gastric fluid resistant, that is a material soluble only

in fluids with a pH greater than that of the stomach. Enteric coating materials include, but are not limited to, cellulose acetate phthalate NF, hydroxypropyl methylcellulose phthalate NF, polyvinyl acetate phthalate NF, and methacrylic acid copolymer NF. Thus, in a low pH environment, the enteric coating will be insoluble and hinder intrusion of water through the semi-permeable membrane which could otherwise dissolve the delay jacket. It may be applied over the semi-permeable membrane using conventional film coating techniques known in the art, for example perforated pan coating.

Upon ingestion, the drug delivery device encounters the acidic gastric fluid, but remains intact because of the enteric coating. After the stomach pushes the device through the pylorus into the duodenum, the device is exposed to fluids of higher pH and the enteric coating dissolves. Once the semi-permeable membrane is exposed to these fluids, the device is activated. Water from the gastro-intestinal tract is imbibed through the membrane by diffusion and begins to selectively dissolve the delay jacket. As the soluble components of this delay jacket are selectively dissolved, they are released either through the membrane, or through the release orifice, until they are depleted. The delay jacket directly under the membrane prevents water from reaching the active drug core, thus providing the delayed release of the active agent. Once the delay jacket has been exhausted of soluble components, a suspension of insoluble material held in place by the membrane, continues to surround the active drug core. Eventually, the active core is reached by the water, increasing the pressure within the membrane as the core osmotic agents imbibe more and more water. As the drug is dissolved or suspended, this hydrostatic pressure forces the active agent through the membrane and/or through the release orifice to deliver the drug at a controlled rate. The release rate of the drug is based on the osmotic properties of the core, the solubility of the drug and excipients, and the water permeation rate through the membrane, and to a more limited extent, the viscosity of the solution or suspension, the suspension of material from the depleted delay jacket, and the size of the membrane pores or release orifice.

As an extension to the basic device, a further layer of active agent may be included to deliver an initial burst of active agent prior to the device reaching the colon. This active agent may be the same as or different from that within the core. The additional active agent layer may be applied over the enteric coating to deliver an immediate release of active agent. Alternatively, this additional layer may be applied under the enteric layer for release in the upper portion of the small intestine.

To deliver active agent intermittently, the basic device is altered by including an additional layer of active agent between the delay jacket and the membrane. This active agent layer comprises an active agent and may optionally include other pharmaceutically acceptable excipients including osmotic agents, lubricants, glidants, wetting agents, binders, fillers, and suspending/thickening agents.

The following examples are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard.

Example 1 - Preparation of colonic delivery device

A colonic delivery device is prepared from the following ingredients:

INGREDIENTS	QUANTITY (mg)
Core	
Metroprolol Fumarate	190
Povidone, USP	22.2
Magnesium Stearate, NF	5.8
Delay jacket	
Dextrates, NF	148
Microcrystalline Cellulose, NF (PH101)	148
Hydroxyethyl Cellulose, NF (250H)	72.15
Magnesium Stearate, NF	1.85
Semi-permeable membrane	
Cellulose acetate, NF (398-10)	3.39
Cellulose acetate, NF (320 S)	23.49
Hydroxypropyl Methylcellulose, USP (15 cps)	1.56
Polyethylene Glycol, NF (3350)	1.56
Enteric coating	
Methacrylic Acid Copolymer, Type C, NF	24.72
Sodium Hydroxide, NF	0.36
Polyethylene Glycol 8000, NF	2.46
Talc, USP	2.46

Metoprolol fumarate and povidone are mixed together and granulated with an aqueous alcohol solution. The granulation is then dried, sized, and blended with magnesium stearate. The dried lubricated powder is compressed into tablet cores using conventional tabletting techniques.

Add the dextrates, microcrystalline cellulose, and hydroxyethyl cellulose to a planetary mixer. Pass the magnesium stearate through a screen and add to mixer. Blend for approximately five minutes.

Add approximately 185 mg of the above mixture to the die cavity of a Colson single-punch tablet press fitted with a 14/32" tablet punch. Place one of the active cores onto the lower layer and add another 185 mg of the mixture. Compress the materials to form a press-coated, jacketed tablet.

Combine 456 mg methylene chloride and 114 mg methyl alcohol on a per tablet basis to form a solution. Dissolve the semi-permeable membrane ingredients in the solution using a propeller type mixer.

Spray coat the jacketed tablets with the above solution in a UniGlatt Coater using the following parameters:

Inlet Air Temperature	45-50°C
Atomizing Air Pressure	2.0 Bar
Spray Rate	15-25 ml/min

Drill the coated tablets with a 0.040" mechanical drill bit using a hand drill and laboratory arrangement.

For 100g of enteric coating dispersion, add 20g of methacrylic acid copolymer to 45.4g of water while mixing. In a second container, mix 0.3g of sodium hydroxide with 6.7g of water and add this mixture to the first container. In a third container, mix 2.0g of polyethylene glycol 8000 with 15.1g of water and add this to the first container. Continue to mix while adding 2.0g of talc and 8.5g of water to form a suspension.

Apply the above suspension to the coated tablets in a Glatt GC 300 12" Perforated Pan Coater using the

following parameters:

Inlet Air Temperature	50-65°C
Atomizing Air Pressure	2.5 Bar
Nozzle Size and Type	1.1 mm, 35°
Spray Rate	15.22 ml/min

Example 2 - Dissolution test

The release rate of a tablet of Example 1 is determined using a two-hour presoak in 0.1N HCl and then a standard dissolution test using USP Rotating Basket and the following parameters:

Stir Rate	100 rpm
Wavelength	275 nm
Temperature	37°C
Medium	0.1 N HCL: 0-2 hr; phosphate buffer (pH=7.5): 2.24 hr

The results of the dissolution test are as follows:

Timepoint (hours)	Total Release (%Total)	Rate (%/hr)
0-2	<0.5	negligible
3-5	<0.5	negligible
6	1.7	1.3
7-8	16.5	7.4
9-10	33.6	8.6
11-12	48.3	7.4
13-14	61.0	6.4
15-18	76.2	3.8
19-24	82.7	1.1

Example 3 - Aqueously administrable semi-permeable membrane

A controlled release delivery device in which the semi-permeable membrane is applied aqueously is prepared from the following ingredients:

INGREDIENTS	QUANTITY
Core	per tablet (mg)
Acetaminophen	80.0
Malitol	98.0
Hydroxypropyl Methylcellulose, 15 cps	10.0
Polyethylene Glycol, 8000	10.0
Magnesium Stearate	2.0
Delay jacket	per tablet (mg)
Dextrates	409.0
Polyethylene Glycol, 8000	23.2
Hydroxypropyl Methylcellulose, 15cps	23.2
Magnesium Stearate	4.6
Semi-permeable membrane	per 1000g dispersion (g)
Cellulose Acetate Latex, 25% (prepared from cellulose acetate, USP)	121.2
Glyceryl Triacetate	45.5
Hydroxypropyl Methylcellulose, 15cps	3.3
Talc	3.3
Deionized Water	826.7

All core components are mixed together and sized. The mixture is then pressed into tablet cores using conventional tabletting techniques.

All delay jacket components are next sized and blended. The jacket is compressed around the drug core by partially filling a larger die cavity of a tablet punch with the jacket blend, placing a tablet core onto this layer and adding further jacket blend to fill the die cavity. The materials are then compressed to form a press-coated, jacketed tablet.

Stir together glyceryl triacetate, hydroxypropyl methylcellulose and talc to form a slurry. Add all of the deionized water while continuing to stir. When a uniform mixture of all components has formed, add the cellulose acetate latex and continue to mix the dispersion. Spray coat the jacket tablets to the desired membrane weight with this dispersion using a perforated pan coater with the following set points:

Nozzle Size	1.0mm Inlet Air
Temperature	68°C
Flowrate	135m^3/h
Pump Rate	10ml/min
Drum Speed	6.5rpm
Atomizing Air Pressure	2.0bar

Drill the coated tablets with a 0.25mm drill-bit to a depth of approximately 1mm.

The above coated tablets can be coated with an enteric dispersion as in example 1.

Example 4 - Preparation of an Intermittent Device

Ingredient	Quantity
Placebo Core	**per tablet (mg)**
dextrates	178.0
hydroxypropyl methylcellulose, 15 cps	10.0
polyethylene glycol 8000	10.0
magnesium stearate	2.0
Drug Sub-coat	**per 1000g of solution (g)**
phenylpropanolamine HCl	126.0
hydroxypropyl methylcellulose, 15 cps	25.0
polyethylene glycol 8000	10.0
deionized water	839.0
Delay Jacket	**per tablet (mg)**
dextrates	409.0
hydroxypropyl methylcellulose, 15 cps	23.2
polyethylene glycol 8000	23.2
magnesium stearate	4.6
Semipermeable Membrane	**per 1000g of dispersion (g)**
cellulose acetate 398-10 (25% aqueous dispersion)	121.2
glyceryl triacetate	45.5
hydroxypropyl methylcellulose, 15 cps	3.3
talc	3.3
deionized water	826.7
Drug Over-coat	**per 1000g of solution (g)**
phenylpropanolamine HCl	98.0
hydroxypropyl methylcellulose, 15 cps	11.0
polyethylene glycol 8000	22.0
deionized water	869.0

All core components are mixed together and sized. The mixture is then pressed into tablet cores using conventional tabletting techniques.

To prepare the sub-coat, heat approximately one-third of the water to near boiling and add the hydroxypropyl methylcellulose followed by the polyethylene glycol with stirring. Remove from heat and add the Phe-

nylpropanolamine HCl followed by the remaining water. Continue to stir until a clear solution is formed. Spray the drug solution onto the placebo cores in a perforated pan coater using the following set-points:

Inlet air temperature	68°C
Air volume flowrate	135m³/h
Pump rate	18.9%
Drum speed	13.5 rpm
Atomizing air pressure	2.00bar
Nozzle size	0.8mm

Stop the process when approximately 32.1mg of drug sub-coat (corresponding to 22.5mg of Phenylpropanolamine HCl) has been applied to the tablets on an individual tablet basis.

The delay jacket and semipermeable membrane are applied as in example 5. The drug over-coat is applied in a manner similar to the drug sub-coat. The coating process is stopped when approximately 30 mg of over-coat is applied (corresponding to 22.5mg of Phenylpropanolamine HCl).

Drill the tablets using a 0.25mm drill bit and a mechanical arrangement to provide a release orifice.

Claims

1. Osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent which comprises:
   a) a solid core containing an active agent;
   b) a delay jacket coated over the core;
   c) a semi-permeable membrane coated over the delay jacket, this membrane optionally having a release orifice; and optionally
   d) an enteric coating over the semi-permeable membrane.

2. The device of claim 1, wherein the delay jacket comprises an osmotic agent.

3. The device of claim 2, wherein the delay jacket further comprises at least one excipient selected from the group consisting of a binder, a hygroscopic suspending or thickening agent, and a tablet lubricant.

4. The device of claim 1, wherein the semi-permeable membrane comprises a compound selected from the group consisting of methacrylic ester copolymers, poly(ethyl acrylate, methyl methacrylate), poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), polymethyl methacrylate-methacrylic acid copolymers, cellulose acetate, ethylcellulose, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate.

5. The device of claim 2, wherein the enteric coating is selected from the group consisting of cellulose acetate phthalate NF, hydroxypropyl methylcellulose phthalate NF, polyvinyl acetate phthalate NF, and methacrylic acid copolymer NF.

6. A process for the preparation of an osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent which comprises:
   a) forming a solid core containing an active agent;
   b) coating said core with a delay jacket;
   c) coating said core with a semi-permeable membrane; and, optionally, applying to this membrane a release orifice; and/or applying
   d) an enteric coating over the semi-permeable membrane.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 81 0212

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	EP-A-0 425 699 (CHUGAI SEIYAKU KABUSHIKI KAISHA) * claim 1 * * page 3, line 1 - line 51 * * page 4, line 30 - line 39 * * page 6; example 8 * -----	1-6	A61K9/28 A61K9/00

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	4 August 1994	Ventura Amat, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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